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Single-Pill Telmisartan and Amlodipine
A Rational Combination for the Treatment of Hypertension

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Abstract

Despite the well documented benefits conferred by adequate control of hypertension, the majority of hypertensive patients display suboptimal control and few patients achieve blood pressure (BP) levels <140/90 mmHg. As a consequence, combination therapy will be required in the majority of patients to achieve target BP. Fixed-dose combinations of antihypertensives not only simplify treatment regimens, contributing to enhanced patient adherence, they provide superior BP-lowering efficacy and an improved tolerability profile. Fixed-dose combinations have become the strategy of choice in high-risk patients or those with stage 2–3 hypertension. The combination of a renin-angiotensin system inhibitor (RASI) with a calcium channel blocker (CCB) is a first-line combination that, in addition to its antihypertensive efficacy, reduces oedema, the main adverse effect of the dihydropyridine CCB and the main factor limiting their use. In morbidity/mortality studies, this fixed-dose combination has also demonstrated superiority over a RASI combined with a diuretic. The single-pill combination of telmisartan and amlodipine has been shown to produce a dose-dependent BP-lowering effect significantly greater than that of either agent administered as monotherapy. These findings have been confirmed by ambulatory BP monitoring in patients with

stage 1 and 2 hypertension, which demonstrated that single-pill telmisartan/amlodipine provides substantial 24-hour BP-lowering efficacy. A higher proportion of patients achieved 24-hour BP goals of <130/80 mmHg on combination therapy. The superior efficacy of combination therapy has been demonstrated across a broad range of patients, including those with moderate-to-severe hypertension, diabetes mellitus and obesity. Moreover, combined use of telmisartan and amlodipine reduces the incidence of amlodipine-induced oedema, making it a preferred combination for the treatment of hypertension.

Hypertension is a well established risk factor for cardiovascular disease. Effective blood pressure (BP) lowering translates into significant reductions in cardiovascular morbidity and mortality rates, irrespective of age or gender.[1,2] To reduce the risk of adverse cardiovascular outcomes, the Joint National Committee (JNC 7)[3] and the European Society of Hypertension/European Society of Cardiology (ESH/ESC),[4] recommend lowering systolic BP (SBP) to below 140 mmHg and diastolic BP (DBP) to below 90 mmHg.

Despite the obvious benefits of controlling BP, only a small proportion of hypertensive patients are adequately treated. In Europe, it is estimated that 73% of hypertensive patients receive no treatment, and only 19–40% of patients on treatment achieve target BP.[5] In Spain, population studies over the last decade show that BP control ranges from 30% to 48%.[6] Data from the primary care setting in Spain demonstrate that BP control improves in parallel to an increase in the use of combination therapy.[7] This review describes the rationale for the combination of a renin-angiotensin system (RAS) inhibitor (RASI) and a calcium channel blocker (CCB) for the treatment of hypertension, and specifically, the combination of telmisartan and amlidipine.

1. The Role of Combination Therapy in Hypertension

International guidelines, supported by evidence from clinical trials, acknowledge that to achieve target BP goals the majority of patients will require combination therapy (figure 1).[3,4,8] A review of large published clinical trials (ALLHAT, LIFE, VALUE, INVEST, ASCOT [see table I for trial definitions]) reported that between 48% and 85% of patients required combination therapy to achieve BP control (<140/90 mmHg).[9] Combination therapy is also recommended in hypertensive patients with co-morbidities such as diabetes mellitus, renal dysfunction or established cardiovascular disease, although a more stringent BP target of <130/80 mmHg is specified.[3,4] Current ESH/ESC guidelines also recommend using combinations of antihypertensive drugs as first-line treatment in patients with concomitant diseases who require rapid BP control and in those requiring a reduction of ≥20 mmHg in SBP or 10 mmHg in DBP.[4]

The optimal combination of antihypertensive agents should provide a superior antihypertensive effect than either agent administered as monotherapy, and have different but complementary mechanisms of action as well as a favourable safety and tolerability profile.

Fixed-dose combinations provide rapid and sustained antihypertensive efficacy and increase the proportion of patients achieving BP control.[10,11] Moreover, studies have shown that fast and effective control of BP may be a determining factor in persistence with long-term treatment.[12,13]

In general, with the exception of angiotensin II type 1 receptor antagonists or blockers (ARBs), the adverse effects associated with antihypertensive drugs tend to increase along with the dose. Fixed-dose combination therapy allows the use of lower doses of the individual components, thereby reducing the likelihood of adverse effects.[14] With non-compliance rates as high as 40%, fixed-dose combination therapy can be expected to increase treatment compliance rates.[15-17] A Cochrane review of 35 studies including 15 000 patients con-

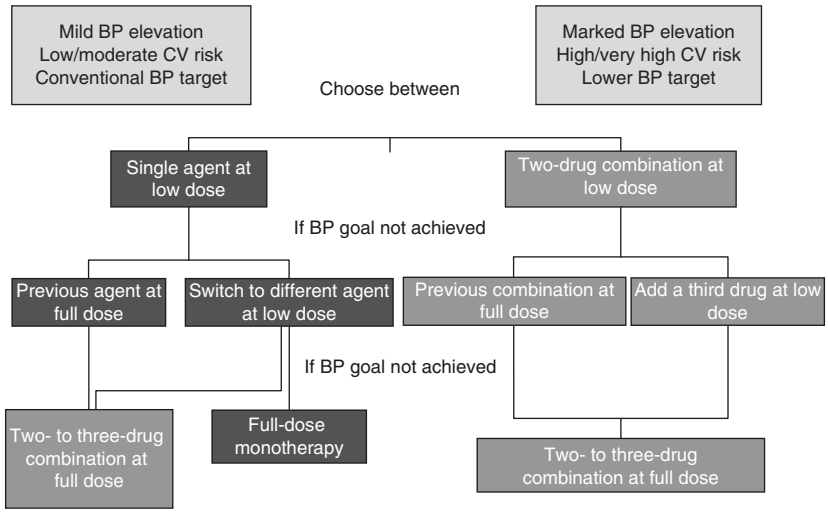

Fig. 1. Treatment strategies for initiating monotherapy or combination therapy in hypertensive patients. Reproduced from the European Society of Hypertension/European Society of Cardiology 2007 Guidelines,[4] with permission. **BP** = blood pressure; **CV** = cardiovascular.

firmed that simplifying treatment is one of the most effective ways to reduce patient non-compliance.[18] These data were corroborated by a comparative review that demonstrated improved adherence to therapy with fixed-dose combinations.[17]

2. Rationale for Combining a Calcium Channel Blocker (CCB) and a Renin-Angiotensin System Inhibitor (RASI)

One of the most commonly used combinations of antihypertensive agents is a RASI and a CCB.[4] Different combinations of RASI with CCB are used but all share similar properties. The advantages of the RASI-CCB combination include the following:[19-23]

- synergistic mechanism of action;
- vascular protective effects due to the improvement in endothelial dysfunction;
- a neutral metabolic profile;
- nephroprotective effect due to its capacity to dilate the renal arterioles;
- reduced incidence of oedema secondary to the use of CCBs;
- greater capacity to reduce morbidity/mortality rates in high-risk hypertensive patients than the RASI-diuretic combination.

2.1 Synergistic Mechanisms of Action

By acting on the two key efferent pathways, the sympathetic nervous system (SNS) and the RAS, the CCB-RASI combination provides effective control of BP through synergistic mechanisms (figure 2).[20,24] CCBs cause vasodilation of the arterioles, activating the SNS, and, as a consequence, the RAS, increasing renin activity and angiotensin II production, which limits the BP-lowering effect of the CCBs.[20,24] The combination of a RASI and a CCB counteracts the stimulation of the RAS.[24] In addition, the antihypertensive efficacy of the RASI is reinforced by the negative sodium balance induced by the CCBs.

This combination not only has synergistic effects in terms of reducing BP, but it may also have BP-independent effects such as vascular protection and improvement in endothelial function (structural/functional changes in resistance arteries, effects on the progression of atherosclerosis and stabilization of plaque, fibrinolysis).[20]

2.2 Efficacy of the RASI-CCB Combination

The ACCOMPLISH study,[25] the first clinical trial to compare two strategies based on a

Table I. Definitions of trial acronyms

Trial names	Definitions
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
CHIEF	Chinese Hypertension Intervention Efficacy
INVEST	INternational VErapamil SR Trandolapril STudy
LIFE	Losartan Intervention For Endpoint reduction in hypertension study
ONTARGET	The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PREVENT	Prevention of Recurrent Venous Thromboembolism
STAR	Saga Telmisartan Aggressive Research study
TEAMSTA Severe HTN	TElmisartan 80 mg plus AMlodipine 10 mg fixed-dose combination tablet STudy versus Amlodipine 10 mg encapsulated tablets or telmisartan 80 mg tablets as first line therapy in patients with Severe HyperTeNsion
TRANSCEND	A randomized placebo-controlled clinical trial evaluating the effects of telmisartan in high risk individuals without heart failure
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation trial

combination of antihypertensives, showed that early use of combination therapy achieves very significant reductions in BP, with post-treatment values averaging 132.5/74.4 mmHg. The strategy based on an ACE inhibitor/CCB (benazepril/amlodipine) combination was superior to the ACE inhibitor/diuretic (benazepril/hydrochlorothiazide) combination in reducing cardiovascular events in high-risk hypertensive patients and reducing the mortality rate by 19.6% ($p < 0.001$). Similarly, the ASCOT-BPLA study, comparing perindopril/amlodipine with atenolol/bendroflumethiazide, found that optimizing control with the combination of a dihydropyridine and a RASI is more effective for primary prevention of cardiovascular events (i.e. stroke, cardiovascular death and all-cause death) than the combination of a β-blocker and a thiazide diuretic.[26] Unfortunately, similar evidence is not available for the combination of ARBs with a CCB. However, there is no reason not to expect a similar benefit.

More recently, the combination of an ARB, such as valsartan or olmesartan, and amlodipine has been evaluated in patients with stage 1 and 2 hypertension, as well as those not controlled by monotherapy.[27,28]

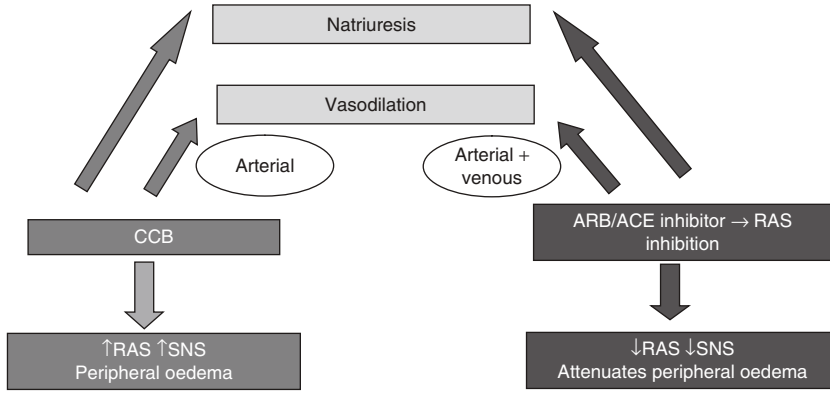

Fig. 2. Synergistic mechanism of action of the combination of a calcium channel blocker (CCB) and a renin-angiotensin system inhibitor (RASI). **ARB** = angiotensin receptor blocker; **CHF** = congestive heart failure; **RAS** = renin-angiotensin system; **SNS** = sympathetic nervous system; ↑ indicates increase; ↓ indicates decrease.

2.3 Metabolic Profile

While both CCBs and ACE inhibitors have a neutral metabolic effect,[29] telmisartan has demonstrated favourable effects on lipid and glucose metabolism.[30] The STAR study demonstrated a significantly more favourable effect when an ACE inhibitor was combined with a CCB versus a diuretic in hypertensive patients with metabolic syndrome.[31] The RASI-CCB combination was also more effective than a β-blocker-diuretic combination in the prevention of new-onset diabetes in the ASCOT study.[26]

2.4 Safety and Tolerability Profile

A number of studies have demonstrated the good safety and tolerability of the combination of a RASI and a CCB. The combination of an ARB and a CCB results in a significant reduction in the incidence of peripheral oedema,[22,32] and cough induced by ACE inhibitors.[22]

2.5 Angiotensin II Receptor Blockers vs ACE Inhibitors for Use in Combination with a CCB

A fixed combination of an ARB/CCB is expected to offer all the advantages of an ACE inhibitor/CCB combination attributable to the inhibition of RAS, which was described earlier in section 2. The rationale for selecting an ARB over an ACE inhibitor for use in combination with a CCB rests largely on differences in safety profile between these classes of RAS inhibitors. ARBs are associated with a lower incidence of cough[33,34] and angioedema[34] than ACE inhibitors.

3. Combination of Telmisartan and Amlodipine

The phase III/IV clinical trial programme with telmisartan/amlodipine consists of nine trials, six of which have been completed. The most important of these studies are reviewed in this section.

3.1 Antihypertensive Efficacy

Data from a double-blind, placebo-controlled, multicentre, dose-finding study in patients with stage 1 or 2 hypertension confirmed the superior efficacy of the telmisartan/amlodipine combination compared with either agent administered as monotherapy.[35] A total of 1461 patients were randomized to one of 16 treatment groups with telmisartan 0, 20, 40, 80 mg and amlodipine 0, 2.5, 5, 10 mg for 8 weeks. Combination therapy consistently resulted in greater reductions in mean BP than monotherapy, irrespective of dose.[35] The greatest reductions in mean SBP/DBP were observed with telmisartan/amlodipine 80/10 mg (26.4/20.1 mmHg; $p < 0.05$) compared with both monotherapies. More than 50% of patients on combination therapy achieved BP control; the highest rates were evident in the telmisartan/amlodipine 80/10 mg group (76.5% [overall control] and 85.3% [DBP control]). Moreover, reductions in BP were shown even in patients with a baseline SBP of >160 mmHg or DBP of ≥110 mmHg (figure 3a and b).[35]

A subanalysis of patients from this study who were considered to be 'difficult to control' (e.g. DBP ≥100 mmHg) demonstrated the efficacy of the telmisartan/amlodipine combination in this patient population, at all clinically relevant doses.[36] Telmisartan/amlodipine provided effective BP lowering of up to 26.5/21.0 mmHg, and 85% of patients achieved DBP control. The reduction in BP was evident after 2 weeks of treatment and was sustained until the end of the trial. Combination therapy with telmisartan/amlodipine was equally effective in patients with elevated SBP (e.g. >160 mmHg).[36]

These results are supported by the TEAMSTA Severe HTN study,[37] which aimed to determine whether the combination of telmisartan/amlodipine 80/10 mg was superior to the single-drug therapies as first-line treatment in 858 patients with severe systolic hypertension (defined as SBP/DBP ≥180/<95 mmHg). Combination therapy resulted in significantly greater BP reductions (47.5/18.7 mmHg vs 36.9/13.8 for telmisartan 80 mg and 43.2/16.3 for amlodipine 10 mg; $p \leq 0.0006$) and higher BP control rates (50.4% vs 35.6% for telmisartan 80 mg and 24.1% for amlodipine 10 mg) than the respective monotherapies.[37] Eighty percent of the maximum effect seen with the combination of telmisartan/amlodipine after 8 weeks was achieved as early as 2 weeks after beginning treatment (a reduction of 37.9 mmHg at 2 weeks vs 47.5 mmHg at 8 weeks).

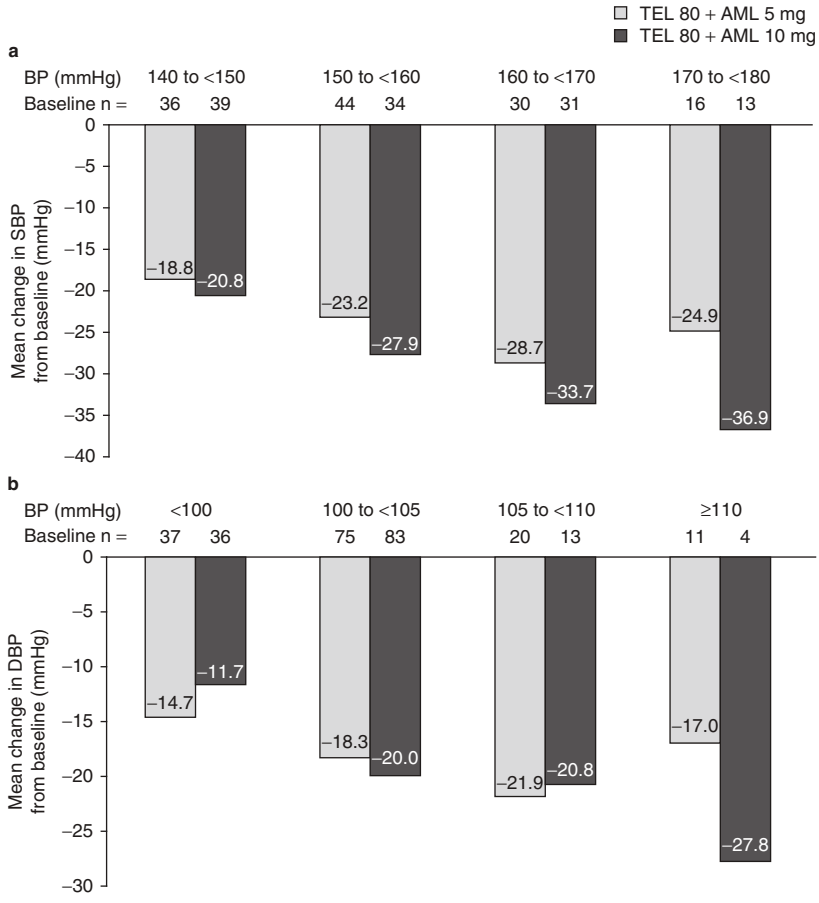

Fig. 3. Reductions in seated trough (**a**) systolic blood pressure (BP) [SBP] and (**b**) diastolic BP (DBP), shown by baseline BP, in adult patients with stage I or II hypertension after 8 weeks' treatment with combination therapy of telmisartan (TEL) 80 mg/day plus amlodipine (AML) 5 or 10 mg/day. Data are not shown for patients with baseline SBP of <140 mmHg or those receiving other dose combinations of TEL plus AML.[35]

The combination of telmisartan/amlodipine affords sustained 24-hour BP control that is superior to that provided by monotherapy as demonstrated in a subgroup of patients enrolled in the dose-finding study.[37] A total of 562 patients with in-clinic DBP of ≥95 and <119 mmHg were randomized to receive telmisartan/amlodipine combination therapy or monotherapy. Ambulatory BP monitoring was performed at baseline and after 8 weeks of treatment. The combination of telmisartan/amlodipine lowered 24-hour BP to a larger extent than the corresponding monotherapies at all doses. At the highest dose (telmisartan/amlodipine 80/10 mg), mean reductions in 24-hour BP were 22.4/14.6 versus 11.9/6.9 mmHg for amlodipine 10 mg and 11.0/6.9 mmHg for telmisartan 80 mg (figure 4; $p < 0.0001$ for each comparison).[38] In addition, BP response and control rates (24-hour BP <130/80 mmHg) were significantly higher with combination therapy (82.7%) versus telmisartan 80 mg (44.2%; $p < 0.0001$) and amlodipine 10 mg (37.9%; $p < 0.0001$).

3.1.1 Efficacy in Hypertensive Patients with Co-Morbidities

The utility of this combination has also been confirmed in hypertensive patients with various co-morbidities.[39,40] In hypertensive patients with

type 2 diabetes (n = 231), the combination of telmisartan/amlodipine was highly effective at reducing BP (response rates 79–96% vs 80–93% for non-diabetic subjects) and achieving clinically relevant BP control (telmisartan/amlodipine 80/10 mg: 87% diabetic vs 74.3% non-diabetic).[39] The greatest mean reductions were generally observed with the telmisartan/amlodipine 80/10 mg (diabetic, 29.1/20.2 mmHg; nondiabetic, 25.1/19.4 mmHg), and telmisartan/amlodipine 40/10 mg (diabetic, 27.3/20.5 mmHg; nondiabetic 23.0/19.5 mmHg) combinations.[39] Importantly, in this patient population, the addition of telmisartan to amlodipine demonstrates a dose-dependent effect on urinary albumin excretion.[41]

Beneficial effects have also been observed in hypertensive patients who were clinically obese (body mass index ≥30 kg/m^2) at baseline (n = 783).[40] In the dose-finding study, a *post hoc* sub-analysis reported that BP control was effectively achieved with combination telmisartan/amlodipine in the majority of the patients, regardless of their weight status. Consistent reductions in DBP and SBP were observed, with the greatest reductions observed at the highest dose combination (telmisartan/amlodipine 80/10 mg). Mean in-clinic baseline BP was 152.8/101.9 mmHg for the obese subgroup and 153.7/101.6 mmHg for the non-obese subgroup (n = 640). Similar BP control rates were reported for obese versus non-obese patients (telmisartan/amlodipine 80/10 mg: 81.7 vs 83.1%, respectively).[40]

3.1.2 Efficacy in Non-Responders to Amlodipine

Switching patients who fail to achieve adequate BP control on antihypertensive monotherapy to combination therapy results in superior BP control rates, suggesting a preferable alternative to increasing the dose of monotherapy.[42,43] The TEAMSTA-5 and -10 studies[42,43] evaluated the efficacy combination telmisartan/amlodipine therapy in hypertensive patients who were not controlled on amlodipine monotherapy. Patients were randomized to telmisartan/amlodipine 40 or 80/5 mg or amlodipine 5 or 10 mg in the TEAMSTA-5 study, and telmisartan/amlodipine 40 or 80/10 mg or amlodipine 10 mg in the TEAMSTA-10 study. In TEAMSTA-5 (n = 1097), telmisartan/amlodipine 80/10 mg resulted in significantly greater BP reductions ($p < 0.001$) and a higher proportion of patients achieved BP control (SBP/DBP <140/<90 mmHg) than amlodipine 10 mg (SBP/DBP 65.7/63.8% vs 54.4/56.7%).[42] Similar results were reported in the TEAMSTA-10 study (n = 1531), where BP control was achieved by a greater proportion of patients receiving single-pill combination therapy (SBP/DBP 60.3/66.5% vs 50.2/51.1% for amlodipine 10 mg monotherapy).[43] Long-term follow-up of both TEAMSTA studies confirm that continued treatment with telmisartan/amlodipine 40 or 80/5 or 10 mg resulted in additional meaningful BP reductions (up to −6.6/−5.5 mmHg), with target BP goals attained in the majority of patients (telmisartan/amlodipine 40–80/10 mg: 81%).[44,45] Across both studies, fewer than

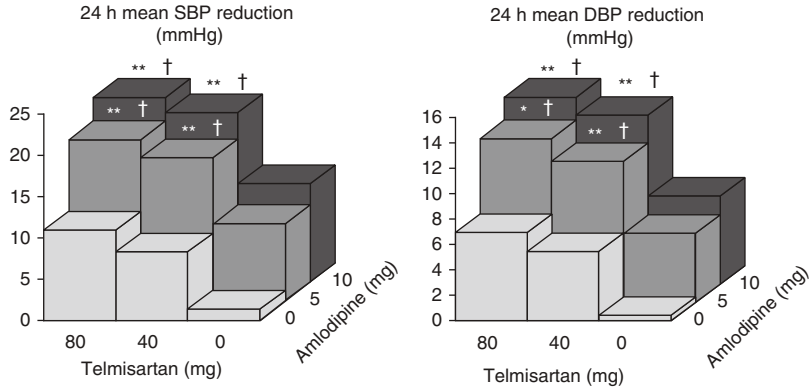

Fig. 4. 24-hour ambulatory blood pressure (BP) monitoring showing the consistent dose response for the combination of telmisartan/amlodipine.[38] **DBP** = diastolic BP; **SBP** = systolic BP; * $p < 0.001$; ** $p < 0.0001$ vs telmisartan alone; † $p < 0.0001$ vs amlodipine alone.

one-quarter of patients required additional antihypertensive medication to achieve BP goals.

The efficacy of the combination of telmisartan/amlodipine compared with amlodipine monotherapy is currently being evaluated in diabetic hypertensive patients (TEAMSTA Diabetes) and in patients who have not achieved the target BP on single-drug therapy with a RASI (direct renin inhibitor [DRI], ACE inhibitor or ARB) [TEAMSTA Switch]. An evaluation of the vascular protective effects of telmisartan/amlodipine, over and above the control of BP, compared with the combination of olmesartan and hydrochlorothiazide is also underway (TEAMSTA Protect). The ongoing CHIEF study, conducted in 13 542 high-risk patients, will provide comparative data on the efficacy of telmisartan/amlodipine compared with the combination of amlodipine plus hydrochlorothiazide in reducing the composite of fatal stroke, non-fatal myocardial infarction (MI) and cardiovascular death.[46]

3.2 Efficacy of Amlodipine and Telmisartan on Cardiovascular Endpoints

While there are no studies investigating morbidity and mortality outcomes with fixed-dose telmisartan/amlodipine, nor any providing data on prognostic outcomes with this combination, the cardioprotective effects of single-agent telmisartan and amlodipine have been documented in a number of studies.

Numerous studies have demonstrated the positive influence of amlodipine on the incidence of cardiovascular events in patients with hypertension and those with ischaemic heart disease.[26,47-51] The CAMELOT study confirmed the beneficial effect of amlodipine on the reduction of cardiovascular events.[48] Relative to ACE-inhibitor therapy, amlodipine reduced the incidence of cardiovascular events (20.2% vs 16.6%) in patients with documented coronary artery disease (CAD). ALLHAT also demonstrated the superiority of amlodipine in the reduction of stroke relative to ACE-inhibitor therapy in this patient population.[50] Evidence from both of these studies also suggests that amlodipine reduces the progression of atherosclerosis.[48,50] The beneficial effect of amlodipine on the primary prevention of cardiovascular events has also been attributed to the early and sustained control of BP.[4] Data suggest that amlodipine may also have BP-independent effects on the reduction of adverse cardiovascular events. Indeed, the PREVENT and the CAMELOT studies were the basis for the indication of amlodipine in CAD, which is independent of BP.[47,48]

The ONTARGET study (n > 25 000) demonstrated that telmisartan was non-inferior to ramipril with regard to the incidence of the composite primary endpoint of cardiovascular death, MI, stroke or hospitalization (16.7% vs 16.5%).[34] Furthermore, the incidence of stroke was similar for both agents, which suggests that telmisartan could be considered for use as a first-line ARB for the treatment of patients at risk for cardiovascular events such as MI or stroke. In TRANSCEND (n > 5900), in patients unable to tolerate ACE inhibitors, telmisartan reduced the risk of the composite outcome of cardiovascular death, MI or stroke by 13% (this composite outcome was only a secondary efficacy endpoint).[52] However, in patients with previous stroke or transient ischaemic attack, telmisartan did not significantly reduce the incidence of recurrent strokes or major cardiovascular events.[53] Given the favourable trend, one possible explanation for these findings was the insufficient study duration of only 2.5 years.

3.3 Safety

In clinical studies, the combination of telmisartan/amlodipine demonstrated an excellent safety and tolerability profile in patients with hypertension. Across all studies, combination therapy consistently reduced the incidence of peripheral oedema relative to amlodipine monotherapy.[35-42] In the dose-finding study, the overall incidence of adverse events was comparable between combination telmisartan/amlodipine (37.9%) and either agent administered as monotherapy (telmisartan [36.8%] or amlodipine [36.1%]).[35] Headache and peripheral oedema were the most frequently reported adverse events. Amlodipine monotherapy (10 mg) was associated with a high incidence of peripheral oedema (17.8%); however, this was substantially reduced with telmisartan/amlodipine

combination therapy (figure 5).[35] The single-pill combination of telmisartan/amlodipine was equally well tolerated over 6 months of follow-up, with similar rates of adverse events reported for telmisartan 40 and 80 mg doses.[44,45] Treatment-related adverse events were reported in up to 8% of patients receiving telmisartan/amlodipine 40 or 80/5 or 10 mg, and low treatment discontinuation rates (≤1.5%) were also reported.[44,45] Peripheral oedema was the most commonly reported treatment-related adverse event, occurring with an incidence of less than eight patients per 100 patient-years at the highest telmisartan/amlodipine dose (80/10 mg).[44]

Combination therapy was also well tolerated in hypertensive patients with co-morbidities. In diabetic hypertensive patients, the incidence of peripheral oedema was estimated to be <2% with telmisartan and amlodipine 5 mg (diabetic, 1.9%; nondiabetic, 1.7%), increasing to 11% in patients receiving combination therapy with amlodipine 10 mg. These figures are significantly lower than those observed in the subjects treated with amlodipine 10 mg alone (diabetic, 21.7%; nondiabetic, 16.7%).[39] In obese patients, rates of oedema were 4.0%, 7.9% and 21.4% compared with 9.4%, 15.2% and 13.6% for non-obese patients receiving telmisartan/amlodipine 40/10 mg, telmisartan/amlodipine 80/10 mg and amlodipine 10 mg, respectively.[40]

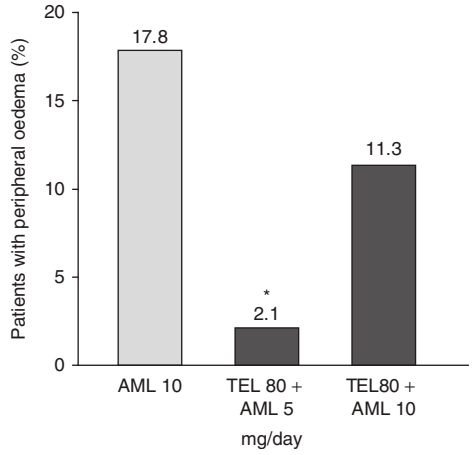

Fig. 5. Incidence of peripheral oedema during 8 weeks' treatment with telmisartan (TEL) 80 mg/day plus amlodipine (AML) 5 mg/day or 10 mg/day compared with AML 10 mg/day as monotherapy, in adult patients with stage I or II hypertension.[35] * $p < 0.0001$ vs A10.[35]

4. Conclusions

Combination therapy will be required in the majority of patients to achieve target BP. Fixed-dose combinations of antihypertensives not only simplify treatment regimens, contributing to enhanced patient adherence, but they also provide superior BP-lowering efficacy, and some may offer an improved tolerability profile. The combination of a RASI with a CCB is a first-line treatment option. The single-pill combination of telmisartan plus amlodipine provides sustained BP lowering in patients with hypertension including those with co-morbidities such as diabetes and obesity. It provides fast and superior BP lowering of up to approximately 50 mmHg and 24-hour BP control in the majority of patients. The addition of telmisartan to amlodipine is well tolerated and substantially offsets the peripheral oedema observed with amlodipine. Although no pharmacoeconomic data are currently available for the single-pill combination of telmisartan plus amlodipine, improved treatment adherence with such a combination is expected to lead to improved treatment outcomes. It remains to be determined whether this combination has the unique cardiovascular-protective effects that are documented for telmisartan and amlodipine, and consequently whether such a fixed-dose combination is cost effective in the long term.

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